厚生労働科学研究費補助金
循環器疾患等生活習慣病対策
総合研究事業

「多目的コホート(JPHCコホート)」における糖尿病・メタボリックシンドロームの発症要因と実態分析に関する研究

(H19−循環器等(生習)−一般−016)

平成21年度 総括研究報告書

研究代表者
野田　光彦　　国立国際医療センター 糖尿病・代謝症候群診療部

研究分担者
井上真奈美　　国立がんセンター がん予防・検診研究センター 予防研究部
磯　　博康　　大阪大学大学院 医学系研究科社会環境医学講座 公衆衛生学
門脇　　孝　　東京大学大学院医学系研究科 糖尿病・代謝内科
溝上　哲也　　国立国際医療センター研究所 国際保健医療研究部
高橋　義彦　　国立国際医療センター 糖尿病・代謝症候群診療部
小久保喜弘　　国立循環器病センター 予防検診部

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の発症要因と実態分析に関する研究

主任研究者　野田　光彦

国立国際医療センター　糖尿病・代謝症候群診療部　部長

研究要旨

従来から厚生労働省がん研究助成金「多目的コホートによるがん・循環器疾患の疫学研究」(現「多目的コホートに基づくがん予防など健康の維持・増進に役立つエビデンスの構築に関する研究」)班(班長 津金昌一郎、以下「厚生労働省多目的コホート研究」班と略)が維持してきたコホートにおいて糖尿病の実態調査、解析を行ってきた。本年度は、精神的ストレスと糖尿病発症との関連、味の好みと肥満との関連、カルシウムやビタミン摂取と糖尿病発症との関連、等につき新たな知見を得た。

今後の研究の成果も踏まえ、本研究による成果が保健指導の具体的、かつエビデンスに基づいた基本的指針となることが期待でき、生活習慣病としての糖尿病、メタボリックシンドローム、及び、これによる血管合併症の予防に貢献し、国民保健・医療経済に寄与するところも大と考える。

分担研究者

井上真奈美　国立がんセンターがん予防・検診研究センター予防研究部　室長

磯　博康　大阪大学大学院医学系研究科　社会環境医学講座公衆衛生学　教授

門脇　孝　東京大学大学院医学研究科　糖尿病・代謝内科　教授

溝上　哲也　国立国際医療センター研究所　国際保健医療研究部　部長

高橋　義彦　国立国際医療センター　糖尿病・代謝症候群診療部　内分泌代謝科医長

小久保喜弘　国立循環器病センター　予防検診部　医長

A. 研究目的

糖尿病は虚血性心疾患や脳卒中(大血管合併症)の危険性を増大し、また、腎症・網膜症・神経障害(細小血管症)による QOL の低下は患者の生活に影響を与える。さらに国民全体と

しての健康レベル、医療経済への影響も大きく、糖尿病対策は生活習慣病の大きなテーマである。本研究では、コホート調査により糖尿病の実態を生活習慣との関係や、循環器疾患、脳卒中や発癌に対するリスクとしての視点から分析し、さらに、糖尿病の発症率を明らかにする。また、糖尿病や冠動脈疾患発症のリスクと考えられているメタボリックシンドロームの実態についても解析を行う。

B. 研究方法

本研究は三つのスキームに大別される。

〈スキーム 1〉

糖尿病をエンドポイントとし、採血データと糖尿病質問票とに基づき、糖尿病有病率の推移、糖尿病発症率と発症要因（生活習慣等）を検討する。これは、ベースライン調査、5 年後調査との比較による。

◆平成 10-12 年度に質問票及び HbA_{1c}、血糖値の測定による調査を行い（ベースライン調査）、糖尿病有病率を把握した。有病率は 50 歳以上では男性約 13%、女性約 7%であった。

◆5 年後（平成 15-17 年度）に再度同様の調査を行い、これにより糖尿病の発症率を把握する。糖尿病の発症は両調査間における HbA_{1c}・血糖値の変化と糖尿病に関する質問票によって定義する。

◆これらを用い生活習慣等との関係を分析する。

◆HbA_{1c} 値については、施設間較差を補正するため、日本糖尿病学会の供与する標準検体によって測定値を較正したものを使用する。平成 10－12 年度は JDS Lot1（HbA_{1c} 5.5%と 10.5%に対応、較正直線に基づく補正）、平成 15－17 年度は JDS Lot2 (HbA_{1c} 4.04、5.38、7.32、9.88、12.63%に対する標準検体、最小二乗法により較正直線を算出して補正）を用いた。較正値はいずれも小数第二位を四捨五入して、小数第一位までとした。

対象地域は沖縄県宮古、高知県中央東、茨城県水戸、長崎県上五島、新潟県柏崎、岩手県二戸、長野県佐久、秋田県横手、沖縄県中部（旧石川の 9 コホート（すなわち、大都市コホートである東京都葛飾区、大阪府吹田市のコホートを除く)。

〈スキーム 2〉

HbA_{1c} 値、糖尿病、メタボリックシンドロームを exposure とし、冠動脈疾患、脳卒中等の血管疾患を主要エンドポイントとした解析を行う。

◆スキーム 1 の対象地域を含む全 10 コホート（健診方法の異なる吹田を除く）において調査を行った。東京都葛飾では 50 歳時の節目健診によるため、平成 12-15 年度の各年度に分けて同じ調査を施行した。

◆糖尿病研究デザインにおける必要なデータを完備した総対象者に対し、糖尿病の虚血性心疾患、脳卒中等の危険因子としての意義を「厚生労働省多目的コホート研究」班の疾患登録システムによる罹患データを用い前向きコホート研究にて解析する。

◆なお、厚生労働省多目的コホート研究」班が追跡している10万人余りの対象者において、癌罹患登録が実施されている。このデータを用いて、糖尿病を曝露要因とした発癌とのかかわりを前向きコホート研究として解析し、糖尿病を有するものでは癌の発症が1.2－1.3倍に増加することをすでに報告している（Inoue M, et al: Arch Intern Med, 2006）。

〈スキーム3〉

自己申告糖尿病に関する解析

対象：コホート対象者のうちの、「厚生労働省多目的コホート班」によるアンケート調査票に回答したもの。

後述のように「多目的コホート」班の調査による自己申告糖尿病の解析（Waki K, et al: Diabetic Med, 2005）によって、糖尿病の家族歴、BMI、加齢とともに、喫煙、飲酒（とくにBMI 22以下の男性）、高血圧の既往が2型糖尿病発症のリスクとなりうることを明らかにした。

平成15-17年度に上記のスキーム1の2回目の調査をすべて施行した。

平成18-19年度は、15-17年度の調査（5年後調査）の集約すなわちデータベースを完成した。それに基づき、ベースライン調査と5年後調査との間の差による糖尿病発症率の検討、ベースライン年齢構成を基準として5年後調査の年齢調整糖尿病有病率を算出し有病率の推移を比較、およびこれと生活習慣との関係について分析を継続している。また、コホートⅡの5地域における5年後調査時点でのメタボリックシンドローム有病率を算出した。

（倫理面への配慮）

健診データの使用に関して、本調査の主旨、秘密保持の厳守等を説明の上、研究目的での健診データの使用とHbA_{1c}測定値、質問票の結果使用に関し、書面により本人自署の同意を得ている。個人情報の管理を厳重に行い、個人同定可能な情報(名前、生年月日、住所等)は解析ファイル等では除外する。研究は疫学研究に関する倫理指針に基づいて行う。もし遺伝情報に関する解析を行う場合は、ヒトゲノム・遺伝子解析研究に関する倫理指針に基づいて行う。

C. 研究結果

1. 本年度の研究成果

本研究は、厚生労働省がん研究助成金「多目的コホートに基づくがん予防など健康の維持・増進に役立つエビデンスの構築に関する研究」班（班長 津金昌一郎；以下「多目的コホート」研究班と略）が維持してきているコホートにおいて糖尿病・メタボリックシンドロームに関する調査、研究を行うもので、研究全体は上述の3つのスキームから成る。これに基づき、本年度は下記の解析結果を論文として報告しているので、その要約を述べる（下記の項目番号は末尾の文献番号に対応している）。なお、各々の成果がどの研究スキームに基づくものであるかを付記した。

1) Kato M, Noda M, Inoue M, Kadowaki T, Tsugane S, for the JPHC Study Group: スキーム 3
Psychological factors and risk of diabetes mellitus among middle-aged Japanese: a population-based prospective study in the JPHC study cohort. Endocrine J 56: 459-468, 2009.
ストレスが血糖値を上昇させる方向に働くことは、病態生理としては確立されているが、精神的ストレスと糖尿病発症との関連をシステマティックに調査した報告には乏しい。本コホートでの 10 年間の追跡（59,791 人）で、男性では日常のストレスが「多い」群では「少ない」群に比較して糖尿病発症は有意に高率であった。女性ではこれは有意ではなかったものの、ストレスの多い生活をする傾向を表すとされるタイプ A 行動パターンの群で、対極的なタイプB行動パターンの群に比較して糖尿病発症のリスクが有意に高まっていた。一方、調査開始時のコーヒー摂取量によって全体を 6 群に分けると、男女ともコーヒー摂取量が多いと糖尿病発症のリスクが低下する有意な傾向が認められ、われわれの、本コホートからのこれまでの報告（Isogawa A, Noda M, Takahashi Y, et al: Lancet 361: 703-704, 2003）を支持するものであった。

2) Matsushita Y, Mizoue T, Takahashi Y, et al; for the JPHC Study Group: スキーム 1
Taste preferences and body weight change in Japanese adults: the JPHC Study. Int J Obes 33: 1191-1197, 2009.
味の好みは人の一生の比較的早期の段階で決定され、生涯にわたって食行動に影響を及ぼしうると考えられるが、味への嗜好と肥満に関する成績はほとんどない。本コホートⅠの男性 13,443 人、女性 15,660 人の合計 29,103 人について、20 歳時からベースライン時までの体重増加の有無と、ベースラインからの 10 年間の体重の変化の双方について、それぞれ味（こってり味、甘い味）の好みとの関係を解析した。
20 歳時からベースライン調査時までの間に 5kg 以上の体重の増加を経験したか否かに関して、こってり味を“好き”、“どちらでもない”とそれぞれ回答した者の、“嫌い”と回答した者に対するオッズ比は、男性、女性ともに有意に高値であった。甘みに関しては、男性では差は全く認められなかったが、女性においては“好き”であると回答した者のオッズ比は“嫌い”と回答した者を基準として 1.22 倍（同：1.09～1.36）であった。
一方、ベースライン時から 10 年後調査時のこってり味、甘みへの嗜好に関する回答別の体重の変化に関しては、10 年間の体重変化量を算出して群間の比較を行った。ベースライン時からその後10年間の体重の変化量は、こってり味に関しては有意差を認めなかったが、甘みに関しては、男女とも“好き”、“どちらでもない”と答えた者は“嫌い”と答えた者に比べて有意な増加が認められた。

3) Kirii K, Mizoue T, Iso H, et al, for the JPHC Study Group: スキーム 3
Calcium, vitamin D, and dairy intake and type 2 diabetes among Japanese. Diabetologia 52: 2542–2550, 2009.

カルシウムやビタミンDの摂取は、糖尿病発症に対して抑制的であることが示唆されてはいるものの、エビデンスには乏しかった。われわれは、これら2つの食事成分と糖尿病発症との関係を、コホートⅠ、Ⅱの5年後の調査時点での食事調査に基づいて、59,796人をその後さらに5年間追跡し、カルシウム、ビタミンDの摂取と2型糖尿病発症との関連を解析した。

女性において乳製品の摂取量が300g/日以上のグループでは、50g/日未満のグループに比べて糖尿病発症のリスクが約30%低かった。また、カルシウムの摂取量が最も多いグループ（約700mg以上）では最も少ないグループ（約400mg未満）に比し約24%リスクの低くなる傾向が、統計的に有意ではないものの認められた。男性ではカルシウム及び乳製品いずれの摂取量も、糖尿病発症との間に関連を認めなかった。

一方、ビタミンD摂取量と糖尿病発症のリスクとの間には、男女ともに統計的に有意な関連をみなかった。しかし、ビタミンDの摂取量によって2群に層別化すると、男女ともにビタミンD摂取量が中央値以上の群においてのみ、カルシウム摂取量が多いと糖尿病発症のリスクが低くなる（男女とも摂取量最大群で最小群の約40%減）という関連が認められた。

4) Nanri A, Mizoue T, Takahashi Y, et al, for the Japan Public Health Center-based Prospective Study Group: スキーム2

Weight change and all-cause, cancer, and cardiovascular disease mortality in Japanese men and women: the Japan Public Health Center-Based Prospective Study. Int J Obes 34: 348-356, 2010.

成人になってからの体重変化と死亡との関係に関してはデータに乏しい。ベースライン調査と5年後調査の間の体重変化とその後の全死亡、がんおよび循環器疾患による死亡との関係を本コホートにおいて検討した。

その結果、699,963人年のフォローアップにおいて4,232人の死亡があり、うち1,872ががん、1,021が循環器疾患による死亡であった。5kg以上の体重減少は、全死亡に関して、体重変化のない者（増減が2.5kg未満の者）に比べた場合のハザード比が、男性において1.62（95%信頼区間：1.45～1.81）、女性において1.76（同：1.51～2.05）であった。一方、5kg以上の体重増加は、男性において1.40（同：1.22～1.59）、女性において1.25（同：1.02～1.54）であった。

5) Nanri A, Mizoue T, Takahashi Y, et al: スキーム3

Soy product and isoflavone intakes are associated with a lower risk of type 2 diabetes in Japanese overweight women. J Nutr 140: 580-586, 2010.

イソフラボンが耐糖能を改善するという動物実験段階での成績が存在するが、疫学研究での結果は一致していない。本コホートにおいて、59,791人を5年間（5年後調査から10年後調査まで）追跡した結果、BMIが25以上の女性において、大豆製品の摂取量が多いと糖尿病の発症率が低い傾向が認められた。

6) Nanri A, Mizoue T, Takahashi Y, et al: スキーム3

Association of weight change in different periods of adulthood with risk of type 2 diabetes in Japanese men and women: the Japan Public Health Center-Based Prospective Study. J Epidemiol Community Health : in press, 2010.

若年期や中年期など異なる期間における体重変化が糖尿病発症リスクに及ぼす影響を検討した研究は少なく、また糖尿病と体重減少との関連は明らかではない。本コホートにおいて、20歳から中年期（ベースライン調査：平均50.6歳）の体重変化及び中年期5年間（ベースライン調査と5年後調査の間）の体重変化と、その後5年間における糖尿病発症との関連を検討した。52,014人を5年間追跡した結果、20歳から体重があまり変化しなかった（5kg未満の増減）群に比べて、増加した（5kg以上）群で男女ともに糖尿病のリスクが有意に上昇していた。また、中年期5年間に体重があまり変化しなかった（2.5kg未満の増減）群に比べて、増加した（5kg以上）群で女性のみ糖尿病のリスクが有意に上昇していた。どちらの期間とも体重減少と糖尿病との有意な関連は認めなかった。

2. 前年度までの研究成果

〈スキーム1〉

このスキームに関しては、コホート全体の年齢調整有病率は、1998～2000年（基準年）には男性で11.8%、女性で6.3%であったが、2003～2005年には男性で14.3%、女性で9.2%であり、この5年間で有病率が2.5～3ポイント上昇したことを確認している。全コホートのベースラインおよび5年後に共通な56～70歳に限ると（6年後の調査を行った上五島地域も5年後調査であるとして算出）、その有病率は、ベースラインでは男性13.2%、女性7.7%、5年後調査では男性16.1%、女性10.7%で、この年代に限っても約3ポイントの有病率の上昇がみられている。

このうち、ともに健診を受診し、かつ採血が朝食前空腹時であった2,137人のデータを用いて空腹血糖値と糖尿病発症［糖尿病は、糖尿病の自己申告、空腹時血糖値 126mg/dl 以上、HbA_{1c}（日本糖尿病学会標準検体較正値）6.1%以上のいずれか1項目以上を有することで定義］との関係を解析すると、糖尿病の発症率は、空腹時血糖値100mg/dl未満では男女とも1,000人年あたり10以下であったが、100～104mg/dlでは男性15、女性22、105～109mg/dlでは男性45、女性33と明らかに上昇しており、正常型の空腹時血糖値とされている110mg/dl未満においても、100～109mg/dlは、この領域にある者について糖尿病発症に関して何らかのワーニングを発するべき血糖域であることが確認された。この後、この領域は日本糖尿病学会により正常高値とされたが、これには本解析結果も判断材料とされている。

他に、各種身体指標（ウエスト（腹囲）、BMI、ウエスト/身長比、ウエスト/ヒップ比）と「リスク重積」との関連や、年齢と体重（BMI）の推移との関係についても報告している。

〈スキーム 2〉

本スキームに関しては、平成 19 年度は、計画書のロードマップに記載したとおり、解析の原資としてのデータベースを予定どおり完成させた（上述の解析にも用いた）。公表に関しては出版物として公表することを予定している。

なお、本スキームの基礎データとしてメタボリックシンドロームの有病率を算出したところ、コホートⅡの 5 地域における 5 年後調査時点で、男性 18.3%、女性 10.8%であった。

メタボリックシンドロームの要素とその集積と、その後のがんの発症（全がんおよび主要部位のがん）との関係、メタボリックシンドロームの要素とその集積と、その後の肝がんの発症との関係についても報告している。

〈スキーム 3〉

「多目的コホート」研究班の調査による自己申告糖尿病の解析（Waki K, et al: Diabetic Med, 2005）によって、糖尿病の家族歴、BMI、加齢とともに、喫煙、飲酒（とくに BMI 22 以下の男性）、高血圧の既往が 2 型糖尿病発症のリスクとなりうることを明らかにしている。上述のように、本年度は精神的ストレス、ビタミン D・カルシウム摂取、イソフラボン摂取等の糖尿病発症への影響について解析を行ない、論文として発表した。

D　考察

糖尿病腎症による人工透析（年間約 15,000 人の新規導入）、糖尿病網膜症による中途失明（年間約 600 人の中途失明）は患者の QOL を大きく損ない、また、糖尿病、メタボリックシンドロームは冠動脈疾患や脳卒中の危険性を増大し、生命予後や生活に多大な影響を与える。のみならず、国民全体の健康レベル、医療経済への影響も大きい。したがって、これらの発症を未然に抑止し、それによってこれら合併症を抑えうる方策を提示することには、保健指導上も医療政策上も重要な意義と必要性がある。

本研究で

(1)糖尿病有病率の推移・発症率

(2)糖尿病の虚血性心疾患や脳卒中、癌に対する発症因子としての関与

(3)糖尿病発症への生活習慣、家族歴、肥満の関与とこれらに基づく保健指導指針

等を知ることができる。我々はすでに、糖尿病の予防を中心に多くのエビデンスを創出してきており［自己申告糖尿病に基づく糖尿病の発症率データ、喫煙、痩せ型男性での飲酒が危険である（いずれも Waki K, et al: Diabetic Med, 2005）、コーヒー摂取が糖尿病発症を抑制する可能性がある（Isogawa A, et al: Lancet, 2003）、など］、今後の研究の成果も踏まえ、本研究による成果が保健指導の具体的、かつエビデンスに基づいた基本的指針となることが期待できる。

糖尿病・メタボリックシンドロームの実態、生活習慣からみた発症要因や、血管合併症との関連の把握は、情報発信・一次予防の観点から必須であり、医療の適正化の見地からも意義

がある。これらに基づく生活習慣改善への国民的啓発と情報の共有化・均霑化は、生活習慣病としての糖尿病、メタボリックシンドローム、及び、これによる血管合併症の予防に貢献し、国民保健・医療経済に寄与するところも大と考える。

E 結論

厚生労働省多目的コホート研究」班が維持してきたコホートにおいて糖尿病の実態調査、解析を行い、本年度は、精神的ストレスと糖尿病発症との関連、味の好みと肥満との関連、カルシウムやビタミン摂取と糖尿病発症との関連、等につき新たな知見を得た。
今後の研究の成果も踏まえ、本研究による成果が保健指導の具体的、かつエビデンスに基づいた基本的指針となることが期待できる。

F 健康危険情報

なし

G 研究発表

発表論文集（※直接本研究の成果であるもののうち、2009年分のみ記載）

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Ⅲ　研究成果の刊行に関する一覧表

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   Association of weight change in different periods of adulthood with risk of type 2 diabetes in Japanese men and women: the Japan Public Health Center-Based Prospective Study.
   J Epidemiol Community Health : in press, 2010.

Ⅳ　研究成果の刊行物・別刷

次頁以降に添付した。

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Psychological Factors, Coffee and Risk of Diabetes Mellitus among Middle-Aged Japanese: a Population-Based Prospective Study in the JPHC Study Cohort

MASAYUKI KATO*, MITSUHIKO NODA**, MANAMI INOUE***, TAKASHI KADOWAKI#, SHOICHIRO TSUGANE***; for the JPHC Study Group

* *Japan Foundation for the Promotion of International Medical Research Cooperation, 1-21-13 Toyama, Shinjuku-ku, Tokyo 162-0052, Japan*

** *Department of Diabetes and Metabolic Medicine, International Medical Center of Japan, 1-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655, Japan*

*** *Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan*

\# *Department of Metabolic Diseases, Graduate School of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan*

Abstract. An association between psychological factors and diabetes has been suspected for a long time. However, epidemiological data on this association is limited. We investigated the association between psychological factors (perceived mental stress and type A behavior) and the onset of diabetes in a community-based, prospective cohort study in a large number of middle-aged Japanese adults. A total of 55,826 subjects (24,826 men and 31,000 women) aged 40-69 years were followed for 10 years. A self-administered questionnaire on medical conditions including diabetes and other lifestyle factors was performed at baseline and 5 and 10 years later. Psychological factors and diabetes were assessed based on the questionnaire results. During the 10-year follow-up period, we documented 1,601 incident cases (6.4%) of diabetes among men and 1,093 cases (3.5%) among women. The risk of diabetes increased with an increasing stress level, especially among men. Multivariate adjusted odds ratios for high stress compared with low stress were 1.36 (1.13 to 1.63) among men and 1.22 (0.98 to 1.51) among women. The risk of diabetes increased with an increasing level of type A behavior only among women. Multivariate adjusted odds ratios for high levels of type A behavior compared with low levels of type A behavior were 1.09 (0.94 to 1.27) among men and 1.22 (1.01 to 1.47) among women. We found an association between perceived mental stress and the incidence of diabetes, especially among men. We also found an association between type A behavior and the incidence of diabetes among women. In addition, inverse association between coffee consumption and the incidence of diabetes which was consistent with other studies was observed.

Key words: diabetes mellitus, perceived mental stress, type A behavior, coffee

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THE PREVALENCE of type 2 diabetes has increased dramatically over the past few decades. Recent estimates indicate that there were 171 million people with diabetes worldwide in the year 2000 and this number is projected to increase to 366 million by 2030 [1]. Diabetes is now one of the main threats to human health and is likely to remain a huge threat to public health in years to come [2].

An association between psychological factors and diabetes has long been suspected [3, 4]. For example, mental stress is thought to deteriorate glucose metabolism through the activation of the hypothalamus-pituitary-adrenal axis (HPA axis) and the sympathetic nervous system [5-8]. Type A behavior pattern is also thought to activate the HPA axis and the sympathetic nervous system. However, epidemiological data about

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Correspondence to: Mitsuhiko NODA, Department of Diabetes and Metabolic Medicine, International Medical Center of Japan, 1-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655, Japan
Abbreviations: HPA, hypothalamus-pituitary-adrenal; JPHC study, The Japan Public Health Centre-based prospective Study; IL-6, interleukin-6; OR, odds ratio; 95% CI, 95% confidence interval.

the association between these psychological factors and diabetes is limited [9-13], and, as far as we know, no study has shown an association between these factors and the incidence of diabetes in a general population. In this paper, we examined the effect of psychological factors (mental stress and type A behavior) on the incidence of diabetes mellitus in a community-based, prospective cohort study in a large number of middle-aged Japanese adults.

Materials and Methods

Subjects and procedures

The Japan Public Health Centre-based prospective Study (JPHC Study) is an ongoing, longitudinal cohort study investigating cancer, cardiovascular diseases and other lifestyle-related diseases. The JPHC Study was launched in 1990 for cohort I and in 1993 for cohort II. Cohort I was composed of five prefectural public health center areas; Ninohe (Iwate Prefecture), Yokote (Akita Prefecture), Saku (Nagano Prefecture), Chubu (Okinawa Prefecture), and Katsushika (metropolitan Tokyo). Cohort II was composed of six prefectural public health center areas; Mito (Ibaraki Prefecture), Nagaoka (Nigata Prefecture), Chuohigashi (Kochi Prefecture), Kamigoto (Nagasaki Prefecture), Miyako (Okinawa Prefecture), and Suita (Osaka Prefecture). The details of the study design have been described elsewhere [14]. The study protocol was approved by the institutional review board of the National Cancer Center, Japan. In the present analysis, two public health center areas (Katsushika and Suita) were excluded because different definitions for the study population were applied. The study population was defined as all registered Japanese inhabitants of the nine public health center areas aged 40–59 years (Cohort I) and 40-69 years (Cohort II) at the beginning of each baseline survey. Each participant completed a self-administered questionnaire that included questions about weight, height, previously diagnosed medical conditions, family history of diabetes, use of drugs, and other lifestyle factors such as physical activity and smoking. This questionnaire also included a food frequency questionnaire that was validated using 28-day diet records [15]. The questionnaire was performed at baseline and 5 and 10 years later. Of the 95,373 individuals (45,452 men and 49,921 women) who completed the baseline questionnaire upon enrolment, 71,713 (75%, 32,369 men and 39,344 women) responded to both of the follow-up questionnaires. We excluded individuals who had any of the following conditions at baseline; cardiovascular disease, chronic liver disease, kidney disease or any type of cancer (n=4,515). Individuals who had missing baseline data for any of the exposure parameters described below were also excluded (n=9,256). Individuals with a body mass index (calculated as weight in kilograms divided by the square of height in meters) of less than 14 or more than 40 were also excluded because of the possibility of unreliable data (n=741). Because the present study examined the incidence of diabetes, we also excluded any subjects with diabetes at baseline (n=3,092). After these exclusions, the remaining cohort consisted of 55,826 participants (24,826 men and 31,000 women).

Assessment of Psychological factors and diabetes

Mental stress was assessed based on three levels of response (low, medium and high) to the question, 'How much stress do you feel in your daily life?' We assessed four aspects of the type A behavioral pattern through self-reports of: competitive drive, speed and impatience, aggressiveness and irritability [16]. These items were assessed by the level (very, somewhat, or not at all) for each question: 'How hasty and impatient do you consider yourself to be?', 'How competitive and eager to excel in everything do you consider yourself to be?', 'How aggressive do you consider yourself to be?', and 'How irritable do you consider yourself to be?'. The above four items were scored from 0 ("not at all") to 2 ("very") and then combined into an overall index of type A behavior pattern. These items matched well with validated instruments such as the Framingham Type A Scale and MMPI-2 Type A Scale in domains such as aggression, irritability, competitiveness and time urgency [16].

We defined subjects with diabetes (diagnosed diabetes) as those who answered 'yes' to the question 'Has a doctor ever told you that you have diabetes?' or 'Do you take any anti-diabetic drugs?'. To document the validity of the diagnosed diabetes, we examined a series of medical records: 94% of the cases of diagnosed diabetes according to the questionnaire were confirmed by medical records [17]. We also conducted a cross-sectional survey in 1990 to examine the sensitivity of diagnosed diabetes according to the criteria

Table 1a. Baseline characteristics of the analysis group according to stress levels.

	Men (n=24,826)			Women (n=31,000)		
	Perceived Mental Stress			Perceived Mental Stress		
	Low (n=3,405)	Medium (n=15,734)	High (n=5,687)	Low (n=4,865)	Medium (n=20,416)	High (n=5,719)
Age	53.3	51.4	48.2	52.9	51.6	49.1
Body Mass Index	23.7	23.5	23.5	23.6	23.5	23.2
Current smoker	49.2	50.2	55.0	3.9	3.9	6.8
Alcohol drinkers*	66.1	67.4	70.1	10.1	9.5	14.0
Alcohol intake among drinkers (g/week)	270.9	264.9	265.9	79.6	79.0	88.4
Family history of diabetes (yes)	8.3	7.9	10.6	8.6	8.4	10.4
Physical activity (yes)	22.0	18.3	17.1	22.0	16.6	13.0
History of hypertension (yes)	17.3	17.2	16.7	16.0	16.5	14.9
Coffee (≥3 cups/day)	12.3	11.5	19.1	8.6	7.9	13.3
Hours of sleep	7.6	7.5	7.2	7.3	7.2	6.9
Level of Type A behavior pattern index						
1 (most Type A)	21.3	22.1	36.1	12.1	13.6	26.5
2	15.7	16.2	16.8	13.6	15.3	18.7
3	35.2	42.0	28.2	39.3	46.7	30.9
4 (most Type B)	27.8	19.7	18.9	35.0	24.5	23.9

Age, body mass index, alcohol intake and hours of sleep are represented as the mean, and the other variables are proportion (%).
*Alcohol drinkers: drinking alcohol ≥ 1 day/week

at that time for subjects (health checkup participants) whose plasma glucose data were available. Among the 6,118 subjects, 248 subjects had diagnosed diabetes. Among the 5,927 subjects who did not have diagnosed diabetes, 49 subjects (0.83%) had diabetes according to the commonly used diagnostic standards utilized in Japan in 1990 (fasting plasma glucose ≥ 7.8mmol/ L; casual plasma glucose ≥ 11mmol/ L) [18] based on a single measurement. Taking into account the above mentioned positive predictive value, the sensitivity and specificity of diagnosed diabetes were 82.9% and 99.7%, respectively.

Those who did not have diagnosed diabetes at baseline but who had it at the time of either the 5- or 10-year follow-up questionnaire were defined as incident cases of diabetes.

Statistical Analysis

All analyses were performed using the data from the 55,826 individuals (24,826 men and 31,000 women) who responded to both the 5- and 10-year questionnaires. The cumulative incidence was defined as the number of new cases of diabetes occurring during the 10-year follow up period divided by the number of subjects at risk of developing diabetes at baseline. We carried out a multivariate analysis using logistic regression to assess the risk of diabetes as odds ratios adjusted for potential confounding factors such as age (continuous), body mass index (continuous), smoking status (never smoker, past smoker, or current smoker at < 20 or ≥ 20 cigarettes per day), alcohol intake (non- or infrequent occasional drinkers, or regular drinkers categorized according to weekly alcohol intake), family history of diabetes (at least one parent or one sibling with diabetes), physical activity (participation in sports at least once a week), history of hypertension, and coffee consumption (< 3 or ≥ 3 cups of coffee per day). Type A behavioral pattern was categorized into four groups based on the overall index of type A behavior pattern: very high (scores of 6–8), high (score of 5), medium (score of 4) or low (scores of 0–3). Hours of sleep was also included in the multivariate analysis as categorical variables (≤ 5, 6, 7, 8, and ≥ 9 hours) because this factors may be associated with psychological factors. All analyses were performed separately for men and women.

Results

The baseline characteristics of the analyzed subjects according to stress levels and type A behavioral pattern index are shown in Table 1a and 1b, respec-

Table 1b. Baseline characteristics of the analysis group according to levels of Type A behavior pattern index.

	Men (n=24,826)				Women (n=31,000)			
	Levels of Type A behavior pattern index				Levels of Type A behavior pattern index			
	1(most Type A) (n=6,253)	2 (n=4,043)	3 (n=9,408)	4 (n=5,122)	1 (n=4,886)	2 (n=4,847)	3 (n=13,206)	4 (n=8,061)
Age	50.4	50.8	51.5	50.8	50.5	50.9	52.0	51.1
Body Mass Index	23.6	23.5	23.5	23.5	23.3	23.3	23.4	23.7
Current smoker	53.2	51.5	51.1	48.7	7.3	4.7	3.7	3.7
Alcohol drinkers*	71.4	69.2	67.4	64.2	14.5	12.1	8.8	9.5
Alcohol intake among drinkers (g/week)	290.5	276.0	250.9	253.3	104.7	76.5	72.3	77.6
Family history of diabetes (yes)	9.0	8.8	7.8	9.2	10.1	9.1	8.2	8.8
Physical activity (yes)	19.8	20.3	18.0	16.5	16.9	18.0	16.8	15.9
History of hypertension (yes)	19.2	16.9	16.5	15.8	15.7	16.6	16.4	15.8
Coffee (≥3 cups/day)	15.0	13.1	12.3	13.4	11.3	10.1	8.2	8.4
Hours of sleep	7.4	7.5	7.4	7.4	7.1	7.2	7.2	7.1
Perceived Mental Stress								
Low	11.6	13.2	12.7	18.5	12.1	13.7	14.5	21.1
Medium	55.6	63.1	70.2	60.6	56.9	64.3	72.1	61.9
High	32.8	23.7	17.1	20.9	31.0	22.0	13.4	17.0

Age, body mass index, alcohol intake and hours of sleep are represented as the mean, and the other variables are proportion (%).
*Alcohol drinkers: drinking alcohol ≥ 1 day/week

tively. Compared with the subjects who reported low stress, those who reported higher stress were likely to be younger, smokers, physically inactive and coffee drinkers. Compared with the subjects with low levels of type A index, those with higher levels of type A index were likely to be smokers, alcohol drinkers and coffee drinkers.

During the 10-year follow-up period, we documented 1,601 incident cases (6.4%) of diabetes among men and 1,093 cases (3.5%) among women. The age- and multivariate-adjusted odds ratios for the incidences of diabetes mellitus according to perceived mental stress are shown in Table 2. For men, a significant, dose-response association was observed between perceived mental stress and diabetes. This association remained almost unchanged after adjustments for known risk factors of diabetes, type A and hours of sleep. For women, the risk of diabetes also increased as the stress level increased. However, this association and dose-response relation were slightly weakened after adjustments for known risk factors of diabetes and marginally disappeared after further adjustments for type A and hours of sleep.

The age- and multivariate-adjusted odds ratios for the incidences of diabetes mellitus according to type A index are shown in Table 3. For men, association between type A index and the risk of diabetes was not observed after adjustments for other risk factors of diabetes. For women, risk of diabetes was higher for those with highest level of type A behavior and this association was slightly strengthened after adjustments for known risk factors of diabetes, perceived mental stress and hours of sleep.

As for individual components of type A behavior pattern, high level of impatience, irritability and aggressiveness were associated, although not statistically significant, with the risk of diabetes (Table 4).

Recently, a number of papers have reported the protective effect of coffee against diabetes, and we included coffee consumption as a known risk factor of diabetes in the above analysis. In fact, coffee consumption (≥3 cups of coffee/day) reduced the risk of diabe-

Table 2. Odds ratios for the 10-year incidences of diabetes mellitus according to perceived mental stress

Men

	Perceived Mental Stress						
	Low (n=3,405)		Medium (n=15,734)		High (n=5,687)		
Cases	199		999		403		
Odds ratio (95%CI)							p for trend
Age-adjusted OR	1	(reference)	1.14	(0.97-1.33)	1.38	(1.15-1.65)	< 0.001
Multivariate OR[1]	1	(reference)	1.20	(1.02-1.41)	1.39	(1.16-1.67)	< 0.001
Multivariate OR[2]	1	(reference)	1.19	(1.01-1.40)	1.36	(1.13-1.63)	0.001

Women

	Perceived Mental Stress						
	Low (n=4,865)		Medium (n=20,416)		High (n=5,719)		
Cases	163		720		210		
Odds ratio (95%CI)							p for trend
Age-adjusted OR	1	(reference)	1.11	(0.94-1.32)	1.28	(1.04-1.58)	0.020
Multivariate OR[1]	1	(reference)	1.11	(0.93-1.33)	1.25	(1.01-1.56)	0.038
Multivariate OR[2]	1	(reference)	1.12	(0.94-1.34)	1.22	(0.98-1.51)	0.080

Multivariate OR[1]: adjusted for age + other known risk factors of diabetes (body mass index, smoking status, alcohol drinking, family history of diabetes, physical activity, history of hypertension and coffee consumption)

Multivariate OR[2]: adjusted for age + other known risk factors of diabetes + levels of Type A behavior and hours of sleep.

Table 3. Odds ratios for the 10-year incidences of diabetes mellitus according to levels of Type A behavior pattern index

Men

	Levels of Type A behavior pattern (4 = most Type B, 1 = most Type A)								
	4 (n=5,122)		3 (n=9,408)		2 (n=4,043)		1 (n=6,253)		
Cases	313		599		249		440		
Odds ratio (95%CI)									p for trend
Age-adjusted OR	1	(reference)	1.03	(0.90-1.19)	1.01	(0.85-1.20)	1.17	(1.01-1.36)	0.038
Multivariate OR[1]	1	(reference)	1.06	(0.92-1.23)	1.02	(0.85-1.21)	1.12	(0.96-1.31)	0.20
Multivariate OR[2]	1	(reference)	1.06	(0.91-1.22)	1.00	(0.84-1.20)	1.09	(0.94-1.27)	0.381

Women

	Levels of Type A behavior pattern (4 = most Type B, 1 = most Type A)								
	4 (n=8,061)		3 (n=13,206)		2 (n=4,847)		1 (n=4,886)		
Cases	292		428		169		204		
Odds ratio (95%CI)									p for trend
Age-adjusted OR	1	(reference)	0.86	(0.74-1.00)	0.97	(0.80-1.18)	1.19	(0.99-1.43)	0.044
Multivariate OR[1]	1	(reference)	0.93	(0.80-1.09)	1.05	(0.86-1.27)	1.25	(1.03-1.50)	0.014
Multivariate OR[2]	1	(reference)	0.93	(0.79-1.09)	1.03	(0.85-1.26)	1.22	(1.01-1.47)	0.031

Multivariate OR[1]: adjusted for age + other known risk factors of diabetes (body mass index, smoking status, alcohol drinking, family history of diabetes, physical activity, history of hypertension and coffee consumption)

Multivariate OR[2]: adjusted for age + other known risk factors of diabetes + perceived mental stress and hours of sleep.

Table 4. Odds ratios for the 10-year incidences of diabetes mellitus according to levels of constituent items of Type A behavior pattern index

Men

		Low		Medium		High
Impatience	n	2,932		14,829		7,065
	cases	195		942		464
	Odds ratio (95%CI)	1 (reference)	1.01	(0.85-1.18)	1.02	(0.86-1.22)
Irritability	n	3,024		14,584		7,218
	cases	179		921		501
	Odds ratio (95%CI)	1 (reference)	1.08	(0.92-1.28)	1.14	(0.95-1.37)
Aggressiveness	n	2,885		17,118		4,823
	cases	167		1,079		355
	Odds ratio (95%CI)	1 (reference)	1.05	(0.89-1.25)	1.12	(0.92-1.36)
Competitiveness	n	2,405		17,388		5,033
	cases	172		1,081		348
	Odds ratio (95%CI)	1 (reference)	0.87	(0.73-1.03)	0.90	(0.74-1.09)

Women

		Low		Medium		High
Impatience	n	4,391		19,491		7,118
	cases	160		665		268
	Odds ratio (95%CI)	1 (reference)	1.05	(0.88-1.26)	1.23	(1.00-1.51)
Irritability	n	2,931		22,312		5,757
	cases	107		762		224
	Odds ratio (95%CI)	1 (reference)	0.99	(0.80-1.23)	1.16	(0.91-1.48)
Aggressiveness	n	4,738		21,755		4,507
	cases	155		757		181
	Odds ratio (95%CI)	1 (reference)	0.96	(0.80-1.15)	1.08	(0.87-1.36)
Competitiveness	n	4,101		23,261		3,638
	cases	155		804		134
	Odds ratio (95%CI)	1 (reference)	0.99	(0.83-1.19)	1.01	(0.80-1.29)

adjusted for age, other known risk factors of diabetes (body mass index, smoking status, alcohol drinking, family history of diabetes, physical activity, history of hypertension and coffee consumption), perceived mental stress and hours of sleep

Table 5. Odds ratios for the 10-year incidences of diabetes mellitus according to coffee consumption

Men

	n	cases	Odds Ratio	(95% CI)
almost never (reference)	7,378	540	1	
1–2 days per week	4,703	314	0.93	(0.80-1.08)
3–4 days per week	3,012	184	0.84	(0.71-1.01)
1–2 cups/day	6,417	374	0.84	(0.73-0.97)
3–4 cups/day	2,442	138	0.83	(0.68-1.02)
≥5 cup/day	874	51	0.82	(0.60-1.11)
p for trend			0.006	

Women

	n	cases	Odds Ratio	(95% CI)
almost never (reference)	9,873	429	1	
1–2 days per week	5,975	218	0.90	(0.76-1.06)
3–4 days per week	3,515	127	0.95	(0.77-1.17)
1–2 cups/day	8,836	262	0.81	(0.69-0.96)
3–4 cups/day	2,223	48	0.62	(0.45-0.84)
≥5 cup/day	578	9	0.40	(0.20-0.78)
p for trend			<0.001	

adjusted for age, other known risk factors of diabetes (body mass index, smoking status, alcohol drinking, family history of diabetes, physical activity, history of hypertension), perceived mental stress, levels of Type A behavior and hours of sleep

tes in the present analysis, especially among women [odds ratio and 95% confidence interval were 0.91 (0.77-1.08) for men and 0.63 (0.47-0.83) for women] and there exists dose-response relationship (Table 5). Because coffee is also thought to have a psychological effect as described later in the Discussion section, we also conducted an analysis stratified according to coffee consumption (<3 or ≥3 cups of coffee/day). After adjustments for all of the above-described parameters, the odds ratio (and 95% CI) for medium and high stress compared with low stress were 1.23 (1.03-1.46) and 1.42 (1.16-1.73) for subjects consuming <3 cups of coffee/day (p for trend = 0.001) and 0.93 (0.58-1.47) and 1.01 (0.61-1.67) for subjects consuming ≥3 cups of coffee/day (p for trend = 0.836) for men. For women, these values were 1.14 (0.95-1.37) and 1.20 (0.96-1.51) for subjects consuming <3 cups of coffee/day (p for trend = 0.118) and 0.80 (0.36-1.75) and 1.24 (0.53-2.87) for subjects consuming ≥3 cups of coffee/day (p for trend = 0.427). The association between perceived mental stress and diabetes was observed only among subjects who consumed <3 cups of coffee/day, especially among men. No such effect modification was observed for type A behavior pattern.

Discussion

We found that perceived mental stress was positively associated with the incidence of diabetes mellitus. The association between perceived mental stress and the incidence of diabetes mellitus was evident among men and it was statistically significant after adjustments for known risk factors of diabetes and also after further adjustments for type A behavior and hours of sleep. For women, the association between perceived mental stress and the incidence of diabetes mellitus was slightly weakened after adjustments for known risk factors of diabetes and it was marginally lower than the significant level after further adjustments for type A behavior and hours of sleep. We also found an association between type A behavior and the incidence of diabetes mellitus. In contrast to mental stress, this association was statistically significant only among women. The reason for this difference is unclear. However, one possible explanation is that there could be a difference between men and women in terms of the mutual modification between mental stress and the type A behavior, on the hypothetical basis that the overall mechanisms by which mental stress and type A behavior give rise to diabetes may be overlapping, as discussed below, and may possibly be modifying each other.

An association between mental stress and diabetes has long been suspected [3, 4]. The mechanism by which mental stress causes diabetes is unclear, but the activation of two systems, the hypothalamus-pituitary-adrenal (HPA) axis and the sympathetic nervous system, are suspected to play roles [8, 19]. Activation of the HPA axis and the sympathetic nervous system increases secretion of cortisol and catecholamines, and hence, leads to the deterioration of glucose metabolism. Interleukin-6 (IL-6), which is suspected to play a pathologic role in a range of diseases including diabetes, is secreted during stress and participates in the stress response [20]. In fact, Kiecolt-Glaser reported an association, in caregivers, between chronic stress and increased plasma levels of IL-6 [21]. Other mechanisms such as stress induced activation of inflammatory response and the failed downregulation of corticosteroid production, have also been proposed [22].

Type A behavior is also thought to stimulate the HPA axis and the sympathetic nervous system [23] and an association between type A behavior and hyperglycemia was reported in a few studies [24, 25]. Therefore it is possible that type A behavior is associated with the risk of diabetes; however, there are no papers that report this association as far as we know.

We found an inverse association between coffee consumption and the incidence of diabetes which was consistent with other studies. Similar inverse association between green tea consumption and the incidence of diabetes was also reported [26]. We also analyzed the effect of other beverages such as green tea, black tea or oolong tea; however, we found no clear association between the risk of diabetes and consumption of these beverages. These differences may come from the fact that these beverages contain less functional ingredients than coffee.

We also found a possible effect modification of perceived mental stress by coffee consumption, especially among men. Coffee consumption may have modified the effect of mental stress on diabetes. One possible explanation for the interaction between stress and coffee consumption is that coffee blocks cortisol formation by inhibiting 11β-hydroxysteroid dehydrogenase type 1 activity [27]. In addition, an effect modification between mental stress and coffee was reported in

the case of blood pressure, that is, coffee blunts stress-induced blood pressure increase in habitual coffee drinkers [28]. However, further research on the mechanism of this effect modification, including whether it actually exists, is needed.

The strengths of our study were that (a) it was population-based; (b) it had a relatively large cohort size; (c) it had an adequate follow-up period; and (d) the study measured and included possible confounding factors. Nevertheless, our study also had several limitations. First, the assessment of diabetes mellitus was based on the results of a self-reported questionnaire. As mentioned in the methods section, however, 94% of the diagnosed diabetes identified by this questionnaire were confirmed by medical records, and the sensitivity and specificity of the diagnosed diabetes were 82.6% and 99.7%, respectively. Therefore we think that this assessment procedure was well validated. In previous studies [17, 29] we provided different numbers for these percentages based on the current (since 1999 in Japan) diagnostic criteria [30] to evaluate the usefulness of the self-reported method for detecting real diabetic conditions using the current diagnostic criteria. In this paper, diabetes was diagnosed according to the criteria at that time (year 1990) [18] and this method is appropriate for assessing the reporting validity of diabetes diagnosed in 1990.

Second, perceived mental stress was assessed based on a single simple question, 'How much stress do you feel in your daily life?' The same question was used to investigate the association between mental stress and mortality from cardiovascular disease [31] and colorectal cancer [32]. Similar self-reported stress has been used to examine the association between stress and diseases such as breast cancer [33], stroke [34] and suicide [35]. However, more extensive stress evaluation may reveal the association between mental stress and the incidence of diabetes more precisely, which necessitates future studies.

Several sources of potential bias exist in our study. The follow-up bias does not seem to be important because the follow up percentage (75%) was relatively high and no large differences in the major risk factors for diabetes were observed between the follow-up subjects and the lost-to-follow-up subjects at baseline (for stress, 16% and 64% of the follow-up subjects and 17% and 63% of the lost-to-follow-up subjects reported low and medium stress, respectively). Misclassification with regard to diabetes and exposure might also have caused biases. However, this type of bias in a cohort study generally distorts the results toward null.

Despite these limitations, as far as we know, our study is the first to demonstrate an association between psychological factors and the onset of diabetes in a large-scale cohort study.

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Conflict of Interest

All authors declare that they have no conflict of interest.

Ethical Approval

This study was approved by the institutional review board of the National Cancer Centre of Japan.